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Parallel Solution-Phase Synthesis of Targeted Tyrphostin Libraries with Anticancer Activity

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The combination of semi-automation, an elegant synthesis, and parallel solution-phase synthesis approaches has allowed the development of five targeted, symmetrical tyrphostin compound libraries. These libraries on average are comprised of 12 compounds. Notwithstanding this, low micromolar potent growth inhibitors against HT29 (colorectal carcinoma) and G401 (renal carcinoma) cell lines were discovered. Additionally, significant SAR data was obtained. We noted that the most potent growth inhibitory activity was consistently observed for those analogues that possessed a 2-chlorophenyl (for **10**: $GI_{50\,HT29}$ $5.5 \pm 0.4\,\mu M$, $GI_{50\,G401}$ $2.6 \pm 0.4\,\mu M$; for **23**: $GI_{50\,HT29}$ $2.4 \pm 0.2\,\mu M$, $GI_{50\,G401}$ $1.9 \pm 1\,\mu M$; for **34**: $GI_{50\,HT29}$ $8.8 \pm 3.1\,\mu M$, $GI_{50\,G401}$ $6.2 \pm 2.9\,\mu M$; for **46**: $GI_{50\,HT29}$ $5.2 \pm 0.9\,\mu M$, $GI_{50\,G401}$ $3.7 \pm 0.6\,\mu M$; for **57**: $GI_{50\,HT29}$ $4.6 \pm 0.8\,\mu M$, $GI_{50\,G401}$ $2.1 \pm 0.2\,\mu M$), a 3-chlorophenyl (for **11**: $GI_{50\,HT29}$ $3.8 \pm 0.7\,\mu M$, $GI_{50\,G401}$ $1.7 \pm 0.7\,\mu M$; for **48**: $GI_{50\,HT29}$ $5.9 \pm 0.1\,\mu M$, $GI_{50\,G401}$ $3.4 \pm 0.6\,\mu M$; for **58**: $GI_{50\,HT29}$ $4.8 \pm 0.9\,\mu M$, $GI_{50\,G401}$ $3.4 \pm 0.2\,\mu M$), or a 3-methoxyphenyl substituent (for **13**: $GI_{50\,HT29}$ $7.4 \pm 3.8\,\mu M$, $GI_{50\,G401}$ $2.8 \pm 0.5\,\mu M$; for **26**: $GI_{50\,HT29}$ $4.5 \pm 0.5\,\mu M$, $GI_{50\,G401}$ $4.9 \pm 1\,\mu M$; for **37**: $GI_{50\,HT29}$ $3.7 \pm 0.2\,\mu M$, $GI_{50\,G401}$ $1.6 \pm 0.2\,\mu M$; for **49**: $GI_{50\,HT29}$ $3.7 \pm 0.4\,\mu M$, $GI_{50\,G401}$ $3.4 \pm 0.2\,\mu M$; for **60**: $GI_{50\,HT29}$ $4.1 \pm 0.6\,\mu M$, $GI_{50\,G401}$ $1.8 \pm 0.3\,\mu M$). Finally, we noted that increasing the distance between the terminal aromatic rings had only a minimal effect on the 2-, 3-chlorophenyl, and 3-methoxyphenyl analogues, but did have a favourable effect on OH, COOH, and multiply substituted analogues.

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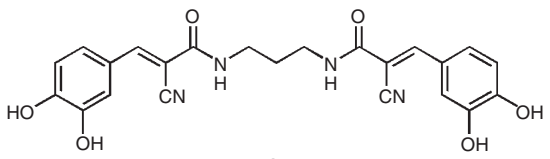
Introduction

More than five decades of research effort in cancer drug discovery and development have provided only 86 new products for the treatment of malignancy.[1] Although major advances have been made in the chemotherapeutic management of some patients, particularly in haematologic malignancies, one-half of all cancer patients either do not respond to therapy, or relapse following initial response and ultimately die from their metastatic disease.[2] For these patients, better systemic therapy offers the only chance for cure or prolonged survival. Discovery of such agents requires continued research into novel therapeutic products that can be used in combination with biological agents and immune therapies in order to eradicate systemic disease not curable by surgery or irradiation.

Understandably, there is considerable pressure to develop new treatments and therapeutic approaches for the treatment of cancer. As part of a series of on-going studies within our laboratories to generate small targeted libraries, which are the first synthetic iteration in the development of new therapeutic agents, we have developed a series of simple synthetic approaches that are amenable to semi-automated, parallel solution-phase synthesis (PSPS). In this particular instance, we have developed methodologies that allow the rapid synthesis of bistyrphostin type molecules **1** (Scheme 1). The tyrphostins are a class of benzylidene malonitrile based compounds developed by Levitski and coworkers.[3] They have been shown to have a diversity of molecular targets, for example tyrosine kinases, GTP-using enzymes, calcinurin, and the AP-2 adaptor complex.[3–6] From the initial discovery of tyrphostins, extensive efforts have stemmed to develop highly potent tyrosine kinase inhibitors such as STI 571 (Glivec), which became the first signal transduction inhibitor to show efficacy in the clinic for chronic



1

Scheme 1.

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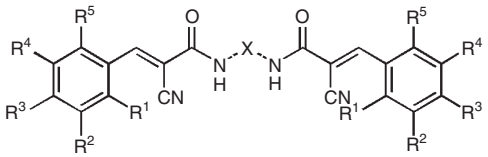
myeloid leukaemia.[7] Bistyrphostin **1** inhibits EGFR tyrosine kinase (IC_{50} 0.4 μM) and blocks EGF cell proliferation (IC_{50} 3 μM).[8] It has also been reported to inhibit HIV integrase,[9] as well as voltage-operated calcium channel currents in vascular smooth muscle cells through inhibition of src tyrosine kinase activity.[10] Given the oncology related success of Glivec and other tyrosine kinase inhibitors, we felt it appropriate to explore the potential of bistyrphostin like compounds developed in our laboratory as anticancer agents.

Tyrphostins were originally synthesized by traditional methods that used individual reactions to yield the desired targets in gramme quantities.[3,8] More recently, other groups have synthesized tyrphostin libraries using solid-phase combinatorial synthesis to produce small quantity libraries (100 mg) of up to 4500 compounds.[11,12] However, we feel that while there have been significant advances in solid-phase synthesis, it is still not routinely available for small laboratories that require specialized techniques, equipment, and approaches. The added cost of materials used in the syntheses, and inevitable wastage, is also a drawback. For these reasons, solution-phase chemistry was deemed to be a more desirable option to be pursued as it has a more traditional organic chemistry basis.

The advantages of using solution-phase chemistry in the development of our bistyrphostin based libraries were twofold. Firstly, application of the Knoevenagel condensation reaction in a similar manner to that used by Levitski in the original synthesis of dimeric tyrphostins[8] would alleviate the need to develop novel chemical methodologies to obtain our compound libraries. Secondly, solution-phase synthesis allows compounds to be produced on a larger scale. Hence, this would allow us to generate around 300 mg of each sample, and thereby allow us to build a comprehensive library of compounds for use in several experiments and biological screens. The main advantage of a solid-phase methodology, namely the ease of purification, was not an issue with our tyrphostin libraries because isolation of the final products was simplified by careful selection of solvents. In particular, the desired products were insoluble in the solvents chosen and, therefore, could be isolated by filtration of the reaction mixtures.

Herein we report the parallel, solution-phase synthesis of compound libraries based upon bistyrphostin **1** and the antitumour activity of these libraries in two human cancer cell lines.

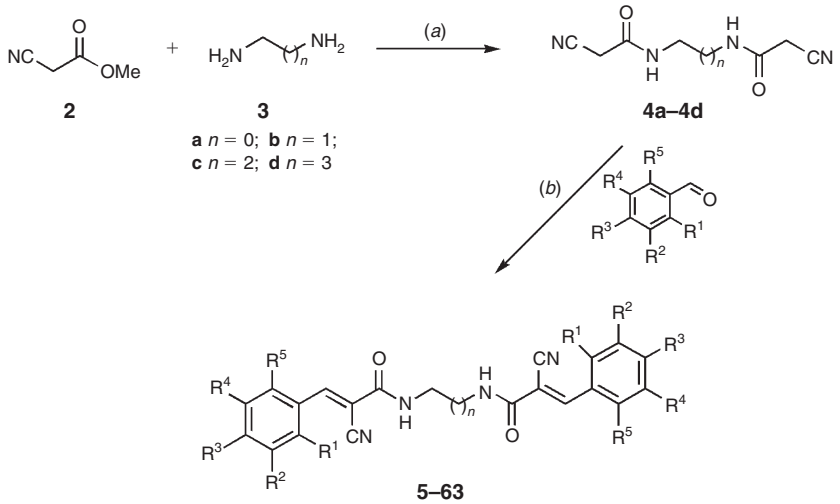


Scheme 2.

Results and Discussion

In this preliminary study towards the development of targeted libraries of tyrphostins, we pursued multiple modifications of both the aromatic nucleus (R^1–R^5) and the linker (X) in **1**. This is shown schematically in Scheme 2.

We and others have previously dissected molecules of this type and developed synthetic pathways to a variety of targets.[8,13] In this work, we commenced from commercially available 1,2-diaminoethane **3a**, which was allowed to react in a solvent-free medium with methyl cyanoacetate **2** to afford the corresponding biscyanoamide **4a** in excellent yield (>90%, Scheme 3). Next, in order to expedite our library development, we conducted a Knoevenagel condensation with a small selection of commercially available benzaldehydes (see Table 1 for details). To further accelerate the library development, these manipulations were conducted using the Büchi Syncore reaction station; this allowed semi-automation of the process. Thus, 12 of the 24 reaction wells available were charged with one equivalent of **3a** in ethanol and a catalytic amount of piperidine, and to these were added



Scheme 3. Reagents and conditions: (*a*) mix, solvent free, 5 min at room temperature; (*b*) piperidine (cat.), (substituted)benzaldehyde, ethanol, reflux, 2 h.

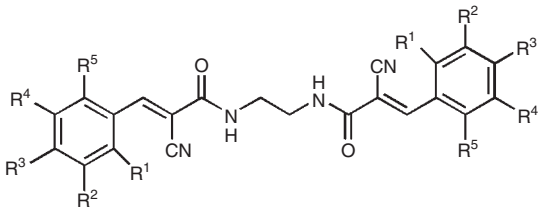
two equivalents of an appropriate benzaldehyde. The mixtures were then heated at reflux for two hours, allowed to cool, and were subsequently filtered, so that the capabilities of the Syncore were exploited. The resultant solids were washed with diethyl ether, refiltered, and dried in situ. Subsequent analysis showed that all the products were greater than 95% pure by NMR spectroscopy.

Upon having successfully accomplished the rapid synthesis of our first 12-compound library, we screened the compounds against two cancer cell lines at 50 μM drug concentrations; HT29 (colorectal carcinoma) and G401 (renal carcinoma). As shown in Table 1, all compounds except **12** and **15** displayed growth inhibition of greater than 50% at this concentration, while compounds, **10**, **11**, and **13** are of particular interest as they showed total growth inhibition of greater than 100%. More detailed analysis afforded GI_{50} values in the low micromolar range (**10**: $GI_{50\,HT29}$ 5.5 ± 0.4 μM, $GI_{50\,G401}$ 2.6 ± 0.4 μM; **11**: $GI_{50\,HT29}$ 3.8 ± 0.7 μM, $GI_{50\,G401}$ 1.7 ± 0.1 μM; **13**: $GI_{50\,HT29}$ 7.4 ± 3.8 μM, $GI_{50\,G401}$ 2.8 ± 0.5 μM).

Both **10** and **11** possess a single chloride substituent in the 2- and 3-position of the aromatic ring, respectively. It is notable that the corresponding 4-chlorophenyl analogue **12** is significantly less potent at inhibiting cell growth (GI_{HT29} 34 ± 5% and GI_{G401} 67 ± 5%). This apparent disfavour of the 4-position is more apparent when the data obtained for the chloride-substituted species is examined in conjunction with that of the other active compound, namely 3-methoxyphenyl **13**. The corresponding 4-methoxy **14**, 3,4-dimethoxy **9**, 3-hydroxy-4-methoxy **15**, and 4-carboxy **16** compounds all display significantly poorer growth inhibition (GI_{HT29} 62 ± 3%, GI_{G401} 62 ± 2%; GI_{HT29} 56 ± 8%, GI_{G401} 68 ± 4%; GI_{HT29} 47 ± 8%, GI_{G401} 74 ± 19%; and GI_{HT29} 58 ± 16%, GI_{G401} 72 ± 21%; respectively at 50 μM drug concentration). These data suggest that either a 2-, 3-chlorophenyl, or a 3-methoxyphenyl substituent plays a positive role in inhibiting cell growth in this type of analogue.

Table 1. Growth inhibition of library 1 against HT29 (colorectal carcinoma) and G401 (renal carcinoma) cell lines

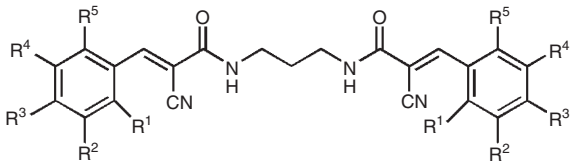
GI [%] is a measure of the percentage growth inhibition relative to untreated control cells after a 72 h exposure to 50 μM of the test compound. As presented, higher values indicate greater growth inhibition. A value greater than 100% is indicative of complete growth inhibition together with cell death.



Compound	R^1	R^2	R^3	R^4	R^5	HT29 GI [%]	G401 GI [%]
5	H	H	H	H	H	73 ± 4	96 ± 15
6	H	OH	H	H	H	61 ± 12	75 ± 4
7	H	H	OH	H	H	53 ± 10	66 ± 4
8	H	OH	OH	H	H	57 ± 19	72 ± 12
9	H	OMe	OMe	H	H	56 ± 8	68 ± 4
10	Cl	H	H	H	H	107 ± 4	105 ± 1
11	H	Cl	H	H	H	115 ± 7	110 ± 5
12	H	H	Cl	H	H	34 ± 5	67 ± 5
13	H	OMe	H	H	H	104 ± 3	106 ± 2
14	H	H	OMe	H	H	62 ± 3	62 ± 2
15	H	OH	OMe	H	H	47 ± 8	74 ± 19
16	H	H	COOH	H	H	58 ± 16	72 ± 21

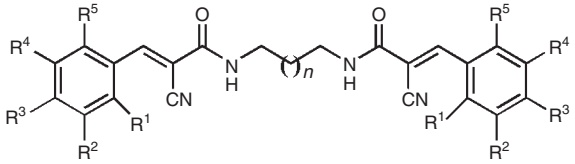
Table 2. Growth inhibition of library 2 against HT29 (colorectal carcinoma) and G401 (renal carcinoma) cell lines

GI [%] is a measure of the percentage growth inhibition relative to untreated control cells after a 72 h exposure to 50 μM of the test compound. As presented, higher values indicate greater growth inhibition. A value greater than 100% is indicative of complete growth inhibition together with cell death. GI_{50} is the concentration of the test drug required to inhibit the cell growth by 50%.



Compound	R^1	R^2	R^3	R^4	R^5	HT29 GI [%]	G401 GI [%]	HT29 GI_{50} [μM]	G401 GI_{50} [μM]
17	H	H	H	H	H	110 ± 5	106 ± 2	12 ± 7.4	6.7 ± 1.5
18	H	OH	H	H	H	110 ± 3	105 ± 1	9.7 ± 0.3	5.7 ± 1.4
19	H	H	OH	H	H	89 ± 4	94 ± 3	21 ± 3.1	11 ± 1.9
20	H	OH	OH	H	H	55 ± 5	67 ± 6	43 ± 3.3	30 ± 8.2
21	H	OH	OH	OH	H	48 ± 8	88 ± 7	58 ± 4.4	25 ± 4.4
22	H	OMe	OH	OH	H	27 ± 9	52 ± 12	103 ± 23	45 ± 10
23	Cl	H	H	H	H	111 ± 3	107 ± 1	2.4 ± 0.2	1.9 ± 1
24	H	Cl	H	H	H	102 ± 5	94 ± 4	28 ± 8.3	14 ± 0.7
25	H	H	Cl	H	H	110 ± 3	107 ± 1	5.0 ± 0.6	5.1 ± 1.2
26	H	OMe	H	H	H	113 ± 5	105 ± 1	4.5 ± 0.5	4.9 + 1
27	H	H	OMe	H	H	54 ± 3	66 ± 4	41 ± 9.8	24 ± 8
28	H	OH	OMe	H	H	94 ± 6	85 ± 4	32 ± 2.8	23 ± 3.3
29	H	H	COOH	H	H	37 ± 5	30 ± 6	82 ± 19	80 ± 12

Table 3. Growth inhibition of libraries 3–5 against HT29 (colorectal carcinoma) and G401 (renal carcinoma) cell lines
GI [%] is a measure of percentage growth inhibition relative to untreated control cells after a 72 h exposure to 50 μM of the test compound. As presented, higher values indicate greater growth inhibition. A value greater than 100% is indicative of complete growth inhibition together with cell death. GI_{50} is the concentration of test drug required to inhibit the cell growth by 50%.



Compound	R^1	R^2	R^3	R^4	R^5	*n*	HT29 GI [%]	G401 GI [%]	HT29 GI_{50} [μM]	G401 GI_{50} [μM]
Library 3										
30	H	H	H	H	H	1	100 ± 7	107 ± 7	2.9 ± 0.2	2.6 ± 0.4
31	H	OH	H	H	H	1	98 ± 7	104 ± 7	6.5 ± 0.3	3.4 ± 0.8
32	H	H	OH	H	H	1	42 ± 7	57 ± 7	–	–
33	H	OH	OH	H	H	1	46 ± 7	82 ± 7	–	–
34	Cl	H	H	H	H	1	114 ± 7	110 ± 7	8.8 ± 3.1	6.2 ± 2.9
35	H	Cl	H	H	H	1	69 ± 7	103 ± 7	28 ± 8.3	14 ± 0.7
36	H	H	Cl	H	H	1	66 ± 7	89 ± 7	–	–
37	H	OMe	H	H	H	1	103 ± 7	105 ± 7	3.7 ± 0.2	1.6 ± 0.2
38	H	H	OMe	H	H	1	35 ± 7	62 ± 7	–	–
39	H	OH	OMe	H	H	1	39 ± 7	55 ± 7	–	–
40	H	H	COOH	H	H	1	92 ± 7	99 ± 7	–	–
Library 4										
41	H	H	H	H	H	2	111 ± 7	106 ± 7	4.9 ± 0.3	3.2 ± 0.2
42	H	OH	H	H	H	2	99 ± 7	107 ± 7	13 ± 5.9	3.9 ± 1
43	H	H	OH	H	H	2	49 ± 7	82 ± 7	–	–
44	H	OH	OH	H	H	2	102 ± 7	101 ± 7	21 ± 2.9	6.2 ± 0.4
45	H	OMe	OMe	H	H	2	42 ± 7	81 ± 7	–	–
46	Cl	H	H	H	H	2	112 ± 7	106 ± 7	5.2 ± 0.9	3.7 ± 0.6
47	H	Cl	H	H	H	2	117 ± 7	106 ± 7	7 ± 1.5	4.7 ± 0.4
48	H	H	Cl	H	H	2	110 ± 7	108 ± 7	5.9 ± 0.1	3.4 ± 0.6
49	H	OMe	H	H	H	2	110 ± 7	109 ± 7	3.7 ± 0.4	3.2 ± 0.2
50	H	H	OMe	H	H	2	86 ± 7	89 ± 7	–	–
51	H	OH	OMe	H	H	2	102 ± 7	94 ± 7	8.3 ± 1.2	3.4 ± 0.3
52	H	H	COOH	H	H	2	104 ± 7	109 ± 7	23 ± 6.1	8.2 ± 1.2
Library 5										
53	H	H	H	H	H	3	107 ± 7	107 ± 7	6.4 ± 1.8	6.0 ± 0.6
54	H	OH	H	H	H	3	72 ± 7	84 ± 7	–	–
55	H	H	OH	H	H	3	64 ± 7	79 ± 7	–	–
56	H	OH	OH	H	H	3	54 ± 7	70 ± 7	–	–
57	Cl	H	H	H	H	3	107 ± 7	106 ± 7	4.6 ± 0.8	2.1 ± 0.2
58	H	Cl	H	H	H	3	76 ± 7	99 ± 7	4.8 ± 0.9	3.4 ± 0.2
59	H	H	Cl	H	H	3	66 ± 7	90 ± 7	–	–
60	H	OMe	H	H	H	3	105 ± 7	105 ± 7	4.1 ± 0.6	1.8 ± 0.3
61	H	H	OMe	H	H	3	28 ± 7	46 ± 7	–	–
62	H	OH	OMe	H	H	3	59 ± 7	77 ± 7	–	–
63	H	H	COOH	H	H	3	36 ± 7	53 ± 7		–

– = GI_{50} not determined.

Also of note in this initial library is that neither of the free hydroxy analogues, **6** nor **7**, are comparatively potent cell growth inhibitors (GI_{HT29} 61 ± 12%, GI_{G401} 75 ± 4%; and GI_{HT29} 53 ± 10%, GI_{G401} 66 ± 4%; respectively).

Given the apparent roles of both Cl and OMe in library 1, we were keen to explore other simple modifications that might be expected to have an impact on growth inhibition. In considering potential modifications, we took into account the ease of compound manipulation using our synthetic approach (Scheme 3) and the utility (and applicability) of the Syncore system. Thus, in this preliminary report we will limit the chemistry and subsequent discussion to a series of small-targeted chain elongation libraries of between 10 and 12 compounds.

Insertion of an additional methylene group proved to be a trivial exercise. Simple substitution of 1,2-diaminoethane (from the synthesis of library 1) with 1,3-diaminopropane afforded the corresponding propane-bridged biscyanoamidoacetate **3b** in excellent yield (>90%). Subsequent manipulations were conducted as described previously, and once again, excellent yields and purities were obtained. Library 2 analogues were then screened against both HT29 and G401 cell lines at a single 50 μM compound dose, as well as at multiple doses in order to produce a dose–response curve from which

a GI_{50} value could be calculated. These data are presented in Table 2.

A preliminary analysis of the percentage growth inhibition values at 50 μM highlighted compounds **17** and **18**, as well as **23**–**26** as being of particular interest (>90% growth inhibition). Moreover, at least one cell line registered complete growth inhibition (>100%). Closer examination of the substituent patterns revealed differences between libraries 1 and 2. Most notable are the free phenyl **17** ($GI_{50\,HT29}$ 12 ± 7.4 and $GI_{50\,G401}$ 6.7 ± 1.5 μM), the 3-hydroxyphenyl **18** ($GI_{50\,HT29}$ 9.7 ± 0.3 and $GI_{50\,G401}$ 5.7 ± 1.4 μM), and the 2- and 4-chlorophenyl **23** and **25** ($GI_{50\,HT29}$ 2.4 ± 0.2 and $GI_{50\,G401}$ 1.9 ± 1 μM; and $GI_{50\,HT29}$ 5.0 ± 0.6 and $GI_{50\,G401}$ 5.1 ± 1.2 μM, respectively), the last chlorophenyl analogues being more potent than the corresponding 3-chlorophenyl analogue **24** ($GI_{50\,HT29}$ 28 ± 8.3 and $GI_{50\,G401}$ 14 ± 0.7 μM). However, the previous observation of excellent growth inhibition associated with the 3-methoxyphenyl analogue **13** was still observed with the methylene extended **26** ($GI_{50\,HT29}$ 4.5 ± 0.5 and $GI_{50\,G401}$ 4.9 ± 1 μM), and to a lesser extent, the corresponding 4-methoxy analogue **27** ($GI_{50\,HT29}$ 41 ± 9.8 and $GI_{50\,G401}$ 24 ± 8 μM). It is also noteworthy that two oxygen-bearing substituents (**20**–**22** and **28**) could be tolerated and were essentially equipotent with **27**.

Our final series of synthetic manipulations involved additional methylene insertions, and each subsequent library was synthesized from 1,4-diaminobutane, 1,5-diaminopentane, and 1,6-diaminohexane, respectively. All synthetic procedures were conducted using the Syncore station as before, and all compounds were synthesized rapidly in high yield and purity. The results of screening against HT29 and G401 carcinoma cell lines are given in Table 3.

Examination of the data presented in Table 3 does not show any major improvements in growth inhibition. Modest improvements in growth inhibition were noted for the free phenyl analogues upon insertion of an additional methylene (compare **17** $GI_{50\,HT29}$ 12 ± 7.4 μM, $GI_{50\,G401}$ 6.7 ± 1.5 μM with **30** $GI_{50\,HT29}$ 2.9 ± 0.2 μM, $GI_{50\,G401}$ 2.6 ± 0.4 μM). However, subsequent methylene insertions had almost no further effect on growth inhibition (**41**: $GI_{50\,HT29}$ 4.9 ± 0.3 μM, $GI_{50\,G401}$ 3.2 ± 0.2 μM; **53**: $GI_{50\,HT29}$ 6.4 ± 1.8 μM, $GI_{50\,G401}$ 6.0 ± 0.6 μM). It should be noted that compound **44** was unusual as it displayed considerably improved potency despite the fact that methylene insertions to give **8**, **20**, and **33** had little effect.

Conclusions

We have developed a facile approach to the rapid synthesis of small-targeted libraries of bioactive compounds. The combination of a good lead compound, simple synthesis, and parallel solution-phase synthesis has allowed the rapid identification of greater than 20 analogues with potent growth inhibition in two cancer derived cell lines, HT29 and G401. This work highlights the utility of PSPS approaches as well as validating the use of small libraries (rather than libraries of hundreds if not thousands of compounds) in the development of more potent bioactive lead compounds. This work is ongoing in our laboratories and new developments will be reported in due course.

Experimental

Biological Evaluation

Cell Culture and Stock Solutions

A 10 mM stock solution in 100% dimethyl sulfoxide [$(CD_3)_2SO$] was prepared for each test compound and stored at 4°C. Further dilutions were made using cell culture media (DMEM, Trace Biosciences) and the final DMSO content was <0.5%. The HT29 (human colon carcinoma) cell line was maintained in DMEM supplemented with 10 mM sodium bicarbonate, while the G401 (human kidney carcinoma) cell line was maintained in McCoys (Trace Biosciences). All culture media was further supplemented with fetal bovine serum (10%), penicillin (100 IU mL^{-1}), streptomycin (100 μg mL^{-1}), and glutamine (4 mM). Cells were passaged every 3–7 days and all cell lines were routinely tested and found to be mycoplasma-free. Both cell lines were cultured in air at 37°C under 5% CO_2.

Cytotoxicity Assay

Cells in logarithmic growth were transferred to 96-well plates. Cytotoxicity was determined by plating cells in triplicate in 100 μL of medium at a density of 2500–3500 cells per well for each cell line. On day zero (24 h after plating), when the cells were in logarithmic growth, 100 μL of medium with or without the test agent was added to each well. After drug exposure for 72 h, growth inhibitory effects were evaluated using the MTT [3-(4,5-dimethyltiazol-2-yl) 2,5-diphenyltetrazolium bromide] assay and absorbance was read at 540 nm. All drugs were initially evaluated at a single drug concentration of 50 μM, from which a GI (%) value was calculated that represented the percentage cell growth inhibition. Compounds that induced appreciable growth inhibition underwent a multiple dose–response assessment from which an IC_{50} value, which represents the drug concentration (μM) that induces 50% growth inhibition, was calculated. All calculations were based on the difference between the optical density values on day zero and those at the end of the drug exposure period.

General

All starting materials were purchased from Aldrich Chemical Co. and Lancaster Synthesis. ^1H and ^{13}C NMR spectra were recorded on a Bruker Advance AMX 300 MHz spectrometer at 300.1315 and 75.4762 MHz, respectively. Chemical shifts are relative to trimethylsilane (TMS) as internal standard. All compounds returned satisfactory analyses.

Synthetic Methods

*2-Cyano-*N*-[3-(2-cyanoacetylamino)ethyl]acetamide* ***4a***

Ethylenediamine **3a** (1.5 g, 25 mmol) and methyl cyanoacetate **2** (5 g, 50 mmol) were stirred at room temperature for 2 h. The resultant white solid was then mixed with ethanol (10 mL) and collected by filtration. Recrystallization from ethanol gave a white solid (6.3 g, 81%), mp 182°C (lit.[8] 183°C). δ_H [$(CD_3)_2SO$] 8.25 (2H, t, *J* 5.5), 3.56 (4H, s), 3.13 (4H, br s). δ_C [$(CD_3)_2SO$] 162.3, 115.9, 38.4, 25.3.

*2-Cyano-*N*-[3-(2-cyanoacetylamino)propyl]acetamide* ***4b***

Propanediamine **3b** (2.2 g, 30 mmol) and methyl cyanoacetate **2** (6.4 g, 65 mmol) were stirred at room temperature for 2 h. The resultant white solid was then mixed with ethanol (20 mL) and collected by filtration. Recrystallization from ethanol gave a white solid (5.0 g, 81%), mp 146°C (lit.[8] 148°C). δ_H [$(CD_3)_2SO$] 8.21 (2H, t, *J* 5.5), 3.59 (4H, s), 3.07 (4H, q, *J* 6.7), 1.53 (2H, quin, *J* 6.7). δ_C [$(CD_3)_2SO$] 162.5, 116.6, 39.3, 28.9, 25.7.

*2-Cyano-*N*-[3-(2-cyanoacetylamino)butyl]acetamide* ***4c***

1,4-Diaminobutane **3c** (3.0 g, 34 mmol) and methyl cyanoacetate **2** (7.0 g, 70 mmol) were stirred at room temperature for 2 h, after which

time a white solid was formed. The solid was then mixed with ethanol (10 mL) and collected by filtration. Recrystallization from ethanol gave a white solid (6.0 g, 78%), mp 145°C (lit.[8] 145°C). δ_H [$(CD_3)_2SO$] 8.15 (2H, t, *J* 5.5), 3.56 (4H, s), 3.05 (4H, br s), 1.38 (4H, br s). δ_C [$(CD_3)_2SO$] 161.8, 116.1, 38.6, 26.1, 25.2.

2-Cyano-N-*[3-(2-cyanoacetylamino)pentyl]acetamide* ***4d***

1,5-Diaminopentane **3d** (2.0 g, 20 mmol) and methyl cyanoacetate **2** (3.9 g, 40 mmol) were stirred at room temperature for 2 h, after which time a white solid was formed. The solid was then mixed with ethanol (10 mL) and collected by filtration. Recrystallization from ethanol gave a white solid (4.62 g, 98%), mp 125°C (lit.[8] 125°C). δ_H [$(CD_3)_2SO$] 8.14 (2H, t, *J* 5.4), 3.55 (4H, s), 3.03 (4H, q, *J* 6.4), 1.39 (4H, quin, *J* 7.0), 1.23 (2H, quin, *J* 7.0). δ_C [$(CD_3)_2SO$] 161.8, 116.1, 38.8, 28.3, 25.2, 23.4

2-Cyano-N-*[3-(2-cyanoacetylamino)hexyl]acetamide* ***4e***

1,6-Diaminohexane **3e** (3.0 g, 26 mmol) and methyl cyanoacetate **2** (6.0 g, 60 mmol) were stirred at room temperature for 2 h, after which time a white solid was formed. The solid was then mixed with ethanol (10 mL) and collected by filtration. Recrystallization from ethanol gave a white solid (6.2 g, 95%), mp 141°C (lit.[8] 140°C). δ_H [$(CD_3)_2SO$] 8.15 (2H, t, *J* 5.5), 3.56 (4H, s), 3.04 (4H, q, *J* 6.1), 1.37 (4H, quin, *J* 5.9), 1.24 (4H, br s). δ_C [$(CD_3)_2SO$] 161.8, 116.1, 38.9, 28.6, 25.8, 25.2

General Procedure for the Synthesis of Targeted Libraries

Each library was prepared from 0.3 M ethanolic stock solutions of each cyanoacetamide (**4a**–**4e**) that contained piperidine (catalytic, 3 drops): **4a** library 1; **4b** library 2; **4c** library 3; **4d** library 4; and **4e** library 5. Each Syncore reaction tube was charged with an aliquot of the appropriate stock solution (5 mL) followed by the appropriate benzaldehyde dissolved in ethanol (5 mL). An example of this is given in the synthesis of **5**, below.

2-Cyano-N-*[2-(2-cyano-3-phenylacryloylamino)ethyl]-3-phenylacrylamide* ***5***

An aliquot of the stock solution generated from 2-cyano-*N*-[3-(2-cyanoacetylamino)ethyl]acetamide **4a** (5 mL) was placed in a Syncore reaction tube followed by benzaldehyde (0.33 g, 3.0 mmol) and ethanol (5 mL). This mixture was then heated at reflux for 2 h, cooled, filtered, and washed with cold diethyl ether (10 mL) to afford a yellow solid (0.45 g, 79%), mp 178–180°C. δ_H [$(CD_3)_2SO$] 8.57 (2H, br t, *J* 5.5), 8.17 (2H, s), 7.92 (4H, m), 7.57 (6H, m), 3.42 (4H, br s). δ_C [$(CD_3)_2SO$] 161.2, 150.5, 132.2, 131.3, 129.9, 129.1, 116.3, 106.4, 38.9.

2-Cyano-N-*{2-[2-cyano-3-(3-hydroxyphenyl)-acryloylamino]ethyl}-3-(3-hydroxyphenyl) acrylamide* ***6***

Synthesized in the manner described for **5** from **4a** and 3-hydroxybenzaldehyde to yield a yellow solid (85%), mp 290–292°C. δ_H [$(CD_3)_2SO$] 8.54 (2H, br t, *J* 5.3), 8.04 (2H, s), 7.36 (4H, m), 7.32 (2H, m), 6.97 (2H, m), 3.38 (4H, br s). δ_C [$(CD_3)_2SO$] 161.8, 158.2, 151.0, 133.5, 130.7, 121.8, 120.1, 116.7, 116.2, 106.5, 39.6.

2-Cyano-N-*{2-[2-cyano-3-(4-hydroxyphenyl)acryloylamino]-ethyl}-3-(4-hydroxyphenyl)acrylamide 7*

This was synthesized in the manner described for **5** from **4a** and 4-hydroxybenzaldehyde to yield a yellow solid (78%), mp > 300°C. δ_H [$(CD_3)_2SO$] 8.36 (2H, br t, *J* 5.5), 8.02 (2H, s), 7.85 (4H, d, *J* 7.2), 6.89 (4H, d, *J* 8.8), 3.36 (4H, br s). δ_C [$(CD_3)_2SO$] 162.3, 150.8, 133.2, 123.2, 117.6, 116.7, 101.5, 39.6.

2-Cyano-N-*{3-[2-cyano-3-(3,4-dihydroxyphenyl)-acryloylamino]ethyl}-3-(3,4-dihydroxyphenyl) acrylamide* ***8***

This was synthesized in the manner described for **5** from **4a** and 3,4-dihydroxybenzaldehyde to yield a yellow solid (81%), mp 290°C (lit.[8] 295°C). δ_H [$(CD_3)_2SO$] 8.32 (2H, t, *J* 5.5), 7.92 (2H, s), 7.53 (2H, d, *J* 2.1), 7.25 (2H, dd, *J* 8.2 and 2.1), 6.85 (2H, d, *J* 2.1), 3.45 (4H, br s). δ_C [$(CD_3)_2SO$] 162.5, 151.0, 161.6, 146.2, 125.8, 123.5, 117.7, 116.5, 116.3, 100.8, 39.6.

2-Cyano-N-*{2-[2-cyano-3-(3,4-dimethoxyphenyl)-acryloylamino]ethyl}-3-(3,4-dimethoxyphenyl)acrylamide* ***9***

This was synthesized in the manner described for **5** from **4a** and 3,4-dimethoxybenzaldehyde to yield a light yellow solid (69%), mp > 300°C. δ_H [$(CD_3)_2SO$] 8.43 (2H, t, *J* 5.5), 8.08 (2H, s), 7.65 (2H, d, *J* 1.9), 7.55 (2H, dd, *J* 9.0 and 2.0), 7.14 (2H, d, *J* 8.6), 3.84 (6H, s), 3.77 (6H, s), 3.31 (4H, br s). δ_C [$(CD_3)_2SO$] 162.1, 152.9, 150.9, 149.1, 125.8, 124.9, 117.5, 112.7, 112.3, 103.0, 56.2, 55.9, 40.2.

3-(2-Chlorophenyl)-N-*{2-[3-(2-chlorophenyl)-2-cyanoacryloylamino]ethyl}-2-cyanoacrylamide* ***10***

This was synthesized in the manner described for **5** from **4a** and 2-chlorobenzaldehyde to yield a yellow solid (83%), mp 248–250°C. δ_H [$(CD_3)_2SO$] 8.70 (2H, br t, *J* 5.6), 8.36 (2H, s), 8.00 (2H, dd, *J* 6.2 and 2.1), 7.62, (2H, m), 7.54 (4H, m), 3.41 (4H, br s). δ_C [$(CD_3)_2SO$] 160.4, 146.8, 134.0, 133.2, 130.3, 130.0, 129.5, 127.7, 115.3, 110.4, 39.1.

3-(3-Chlorophenyl)-N-*{2-[3-(3-chlorophenyl)-2-cyanoacryloylamino]ethyl}-2-cyanoacrylamide* ***11***

This was synthesized in the manner described for **5** from **4a** and 3-chlorobenzaldehyde to yield a light yellow solid (70%), mp 172–174°C. δ_H [$(CD_3)_2SO$] 8.39 (2H, t, *J* 5.3), 7.97 (2H, s), 7.85 (2H, t, *J* 1.9), 7.86 (2H, m), 7.60 (4H, m), 3.45 (4H, br s). δ_C [$(CD_3)_2SO$] 160.9, 148.1, 133.8, 133.7, 131.6, 131.0, 129.0, 115.6, 108.5, 39.5.

3-(4-Chlorophenyl)-N-*{2-[3-(4-chlorophenyl)-2-cyanoacryloylamino]ethyl}-2-cyanoacrylamide* ***12***

This was synthesized in the manner described for **5** from **4a** and 4-chlorobenzaldehyde to yield a yellow solid (76%), mp 244–246°C. δ_H [$(CD_3)_2SO$] 8.58 (2H, br t, *J* 5.5), 8.16 (2H, s), 7.91 (4H, d, *J* 8.6), 7.63 (4H, d, *J* 6.8), 3.32 (4H, br s). δ_C [$(CD_3)_2SO$] 161.0, 149.1, 136.8, 131.6, 130.7, 129.3, 116.0, 106.9, 39.2.

2-Cyano-N-*{2-[2-cyano-3-(3-methoxyphenyl)-acryloylamino]ethyl}-3-(3-methoxyphenyl)acrylamide* ***13***

This was synthesized in the manner described for **5** from **4a** and 3-methoxybenzaldehyde to yield a yellow solid (65%), mp 118–120°C. δ_H [$(CD_3)_2SO$] 8.57 (2H, br t, *J* 5.4), 8.14 (2H, s), 7.49 (2H, m), 7.47 (2H, m), 7.15 (4H, m), 3.79 (6H, br s), 3.98 (4H, br s). δ_C [$(CD_3)_2SO$] 161.2, 159.4, 150.4, 133.1, 130.3, 122.3, 118.1, 116.3, 114.7, 106.5, 55.2, 39.4.

2-Cyano-N-*{2-[2-cyano-3-(4-methoxyphenyl)acryloylamino]-ethyl}-3-(4-methoxyphenyl)acrylamide* ***14***

This was synthesized in the manner described for **5** from **4a** and 4-methoxybenzaldehyde to yield a yellow solid (94%), mp 246–248°C. δ_H [$(CD_3)_2SO$] 8.43 (2H, br t, *J* 5.5), 8.09 (2H, s), 7.95 (4H, d, *J* 8.9), 7.12 (4H, d, *J* 8.9), 3.84 (6H, s), 3.36 (4H, br s). δ_C [$(CD_3)_2SO$] 163.0, 162.1, 150.5, 132.8, 124.8, 117.4, 115.2, 103.1, 56.0, 40.2.

2-Cyano-N-*{2-[2-cyano-3-(3-hydroxy-4-methoxyphenyl)-acryloylamino]ethyl}-3-(3-hydroxy-4-methoxyphenyl)-acrylamide* ***15***

This was synthesized in the manner described for **5** from **4a** and 3-hydroxy-4-methoxybenzaldehyde to yield a bright yellow solid (98%), mp 274–276°C. δ_H [$(CD_3)_2SO$] 8.40 (2H, br t, *J* 5.6), 7.97 (2H, s), 7.53 (2H, d, *J* 2.0), 7.37 (4H, dd, *J* 8.6 and 2.1), 7.06 (4H, d, *J* 8.6), 3.84 (6H, s), 3.36 (4H, br s). δ_H [$(CD_3)_2SO$] 161.8, 151.7, 150.3, 146.7, 124.5, 116.8, 115.4, 112.0, 102.2, 55.6, 39.1.

2-Cyano-N-*{2-[2-cyano-3-(4-carboxyphenyl)acryloylamino]-ethyl}-3-(4-carboxyphenyl)acrylamide* ***16***

This was synthesized in the manner described for **5** from **4a** and 4-carboxybenzaldehyde to yield a yellow solid (96%), mp > 300°C.

δ_H [$(CD_3)_2SO$] 8.68 (2H, t, *J* 5.3), 8.21 (2H, s), 8.00 (4H, d, *J* 8.0), 7.97 (4H, d, *J* 8.1), 3.40 (4H, br s). δ_C [$(CD_3)_2SO$] 166.7, 162.4, 161.0, 149.4, 135.3, 134.3, 129.8, 129.8, 116.1, 115.9, 108.2.

2-Cyano-N-*[3-(2-cyano-3-phenylacryloylamino)-propyl]-3-phenylacrylamide* ***17***

This was synthesized in the manner described for **5** from **4b** and benzaldehyde to yield a yellow solid (81%), mp 138–140°C. δ_H [$(CD_3)_2SO$] 8.37 (2H, s), 7.95 (4H, d, *J* 6.8), 7.52 (6H, m) 7.12 (2H, br t, *J* 5.5), 3.53 (4H, q, *J* 6.0), 1.70 (2H, br quin, *J* 6.1). δ_C [$(CD_3)_2SO$] 161.1, 153.2, 132.7, 131.7, 130.6, 129.2, 116.8, 103.8, 37.1, 29.5.

2-Cyano-N-*{3-[2-cyano-3-(3-hydroxyphenyl)acryloylamino]-propyl}-3-(3-hydroxyphenyl)acrylamide* ***18***

This was synthesized in the manner described for **5** from **4b** and 3-hydroxybenzaldehyde to yield a yellow solid (71%), mp 212–216°C. δ_H [$(CD_3)_2SO$] 8.43 (2H, t, *J* 5.5), 8.05 (2H, s), 7.35 (4H, m), 7.33 (2H, m), 6.96 (2H, m), 3.26 (4H, q, *J* 6.1), 1.75 (4H, quin, *J* 6.8). δ_C [$(CD_3)_2SO$] 161.4, 158.2, 151.0, 133.5, 130.7, 121.8, 120.1, 116.7, 116.2, 106.3, 37.9, 29.1.

2-Cyano-N-*{3-[2-cyano-3-(4-hydroxyphenyl)acryloylamino]-propyl}-3-(4-hydroxyphenyl)acrylamide* ***19***

This was synthesized in the manner described for **5** from **4b** and 4-hydroxybenzaldehyde to yield a yellow solid (58%), mp 250–252°C. δ_H [$(CD_3)_2SO$] 8.28 (2H, t, *J* 5.5), 8.03 (2H, s), 7.85 (4H, d, *J* 8.8), 6.90 (4H, d, *J* 8.7), 3.23 (4H, q, *J* 6.1), 1.71 (2H, quin, *J* 6.7). δ_C [$(CD_3)_2SO$] 162.2, 161.9, 150.8, 133.3, 123.3, 117.6, 116.6, 101.4, 37.8, 29.2.

2-Cyano-N-*{3-[2-cyano-3-(3,4-dihydroxyphenyl)acryloylamino]-propyl}-3-(3,4-dihydroxyphenyl)acrylamide* ***20***

This was synthesized in the manner described for **5** from **4b** and 3,4-dihydroxybenzaldehyde to yield a yellow solid (85%), mp 274°C (lit.[9] 277°C). δ_H [$(CD_3)_2SO$] 8.24 (2H, br t, *J* 5.5), 7.92 (2H, s), 7.52 (2H, d, *J* 2.1), 7.26 (2H, dd, *J* 8.2 and 2.1), 6.85 (2H, d, *J* 8.2), 3.23 (4H, q, *J* 6.0), 1.70 (2H, quin, *J* 6.7). δ_C [$(CD_3)_2SO$] 161.5, 150.6, 150.5, 125.1, 123.2, 117.1, 116.0, 115.8, 100.5, 37.3, 28.8.

2-Cyano-N-*{3-[2-cyano-3-(3,4,5-trihydroxyphenyl)acryloylamino]-propyl}-3-(3,4,5-trihydroxyphenyl)acrylamide* ***21***

This was synthesized in the manner described for **5** from **4b** and 3,4,5-trihydroxybenzaldehyde to yield a yellow solid (70%), mp > 300°C (lit.[9] > 300°C). δ_H [$(CD_3)_2SO$] 8.18 (2H, t, *J* 5.5), 7.78 (2H, s), 6.99 (4H, s), 3.21 (4H, q, *J* 6.8), 1.68 (2H, quin, *J* 6.8). δ_C [$(CD_3)_2SO$] 161.8, 150.7, 145.9, 140.3, 121.2, 117.3, 109.9, 99.5, 38.2, 28.9.

2-Cyano-N-*{3-[2-cyano-3-(3,4-dihydroxy-5-methoxyphenyl)-acryloylamino]propyl}-3-(3,4-dihydroxy-5-methoxyphenyl)-acrylamide* ***22***

This was synthesized in the manner described for **5** from **4b** and 3,4-dihydroxy-5-methoxybenzaldehyde to yield an orange solid (42%), mp > 300°C. δ_H [$(CD_3)_2SO$] 8.35 (2H, t, *J* 5.4), 7.95 (2H, s), 7.21 (2H, d, *J* 1.9), 7.12 (2H, d, *J* 1.9), 3.21 (4H, q, *J* 6.8), 1.71 (2H, quin, *J* 6.8). δ_C [$(CD_3)_2SO$] 161.3, 150.6, 147.2, 145.3, 121.0, 117.6, 110.6, 107.6, 98.7, 38.4, 28.9.

3-(2-Chlorophenyl)-N-*{3-[3-(2-chlorophenyl)-2-cyanoacryloylamino]propyl}-2-cyanoacrylamide* ***23***

This was synthesized in the manner described for **5** from **4b** and 2-chlorobenzaldehyde to yield a yellow solid (80%), mp 172–174°C. δ_H [$(CD_3)_2SO$] 8.57 (2H, br t, *J* 5.4), 8.36 (2H, s), 7.98 (2H, dd, *J* 4.1 and 2.1), 7.52 (6H, m), 3.32 (4H, q, *J* 6.0), 1.77 (2H, quin, *J* 6.5). δ_C [$(CD_3)_2SO$] 159.9, 146.8, 134.0, 133.2, 130.3, 130.0, 129.6, 127.7, 115.3, 110.3, 37.6, 28.4.

3-(4-Chlorophenyl)-N-*{3-[3-(4-chlorophenyl)-2-cyanoacryloylamino]propyl}-2-cyanoacrylamide* ***24***

This was synthesized in the manner described for **5** from **4b** and 3-chlorobenzaldehyde to yield a yellow solid (81%), mp 156–158°C. δ_H [$(CD_3)_2SO$] 8.49 (2H, t, *J* 5.6), 8.15 (2H, s), 7.95 (2H, t, *J* 1.8), 7.85 (2H, m), 6.96 (4H, m), 3.27 (4H, q, *J* 6.7), 1.76 (2H, quin, *J* 6.8). δ_C [$(CD_3)_2SO$] 160.4, 148.9, 133.9, 133.7, 131.7, 131.0, 130.9, 129.2, 128.3, 115.8, 107.9, 37.6, 28.4.

3-(4-Chlorophenyl)-N-*{3-[3-(4-chlorophenyl)-2-cyanoacryloylamino]propyl}-2-cyanoacrylamide* ***25***

This was synthesized in the manner described for **5** from **4b** and 4-chlorobenzaldehyde to yield a yellow solid (87%), mp 168–172°C. δ_H [$(CD_3)_2SO$] 8.47 (2H, t, *J* 5.3), 8.15 (2H, s), 7.92 (4H, d, *J* 8.4), 7.60 (4H, d, *J* 8.4), 3.29 (4H, q, *J* 5.9), 1.76 (2H, quin, *J* 6.5). δ_C [$(CD_3)_2SO$] 160.6, 149.1, 136.8, 131.6, 130.7, 129.2, 116.1, 106.8, 37.5, 28.5.

2-Cyano-N-*{3-[2-cyano-3-(3-methoxyphenyl)acryloylamino]-propyl}-3-(3-methoxyphenyl)acrylamide* ***26***

This was synthesized in the manner described for **5** from **4b** and 3-methoxybenzaldehyde to yield a yellow solid (59%), mp 132–134°C. δ_H [$(CD_3)_2SO$] 8.46 (2H, t, *J* 5.4), 8.14, (1H, s), 7.50 (2H, s), 7.44 (4H, m), 7.13 (2H, t, *J* 7.5), 3.78 (6H, s), 3.29 (4H, q, *J* 5.6), 1.77 (2H, quin, *J* 6.3). δ_C [$(CD_3)_2SO$] 160.8, 159.3, 150.4, 133.1, 130.2, 122.3, 118.1, 116.3, 106.4, 55.2, 37.5, 28.5.

2-Cyano-N-*{3-[2-cyano-3-(4-methoxyphenyl)acryloylamino]-propyl}-3-(4-methoxyphenyl)acrylamide* ***27***

This was synthesized in the manner described for **5** from **4b** and 4-methoxybenzaldehyde to yield a yellow solid (88%), mp 190–192°C. δ_H [$(CD_3)_2SO$] 8.31 (2H, t, *J* 5.2), 8.08 (2H, s), 7.93 (4H, d, *J* 8.6), 7.10 (4H, d, *J* 8.6), 3.83 (6H, s), 3.27 (4H, q, *J* 5.8), 1.74 (2H, quin, *J* 6.3). δ_C [$(CD_3)_2SO$] 162.5, 161.2, 150.0, 132.4, 124.3, 116.9, 114.7, 102.4, 55.5, 37.4, 28.7.

2-Cyano-N-*{3-[2-cyano-3-(3-hydroxy-4-methoxyphenyl)-acryloylamino]propyl}-3-(3-hydroxy-4-methoxyphenyl)-acrylamide* ***28***

This was synthesized in the manner described for **5** from **4b** and 3-hydroxy-4-methoxybenzaldehyde to yield a yellow solid (50%), mp 194–196°C. δ_H [$(CD_3)_2SO$] 8.28 (2H, t, *J* 5.1), 7.98 (2H, s), 7.53 (2H, d, *J* 1.6), 7.36 (2H, dd, *J* 8.3 and 1.5), 7.04 (2H, d, *J* 8.5), 3.84 (6H, s), 3.26 (4H, q, *J* 5.6), 1.73 (2H, quin, *J* 6.5). δ_C [$(CD_3)_2SO$] 161.4, 151.7, 150.4, 146.7, 124.5, 124.5, 116.5, 114.5, 111.9, 102.1, 102.0, 55.6, 37.4, 28.7.

2-Cyano-N-*{3-[2-cyano-3-(4-carboxyphenyl)acryloylamino]-propyl}-3-(4-carboxyphenyl)acrylamide* ***29***

This was synthesized in the manner described for **5** from **4b** and 4-carboxybenzaldehyde to yield a white solid (82%), mp 260–264°C. δ_H [$(CD_3)_2SO$] 8.62 (2H, t, *J* 5.3), 8.31 (2H, s), 8.10 (4H, d, *J* 8.0), 7.98 (4H, d, *J* 8.1), 3.23 (4H, q, *J* 5.7), 1.75 (2H, quin, *J* 6.6). δ_C [$(CD_3)_2SO$] 166.7, 162.4, 161.0, 149.4, 135.3, 134.3, 129.8, 129.8, 116.1, 115.9, 108.2, 39.4, 26.2.

2-Cyano-N-*[4-(2-cyano-3-phenylacryloylamino)butyl]-3-phenylacrylamide* ***30***

This was synthesized in the manner described for **5** from **4c** and benzaldehyde to yield a yellow solid (85%), mp 188–190°C. δ_H [$(CD_3)_2SO$] 8.51 (2H, t, *J* 5.6), 7.94 (2H, s), 7.92 (4H, m), 7.56 (6H, m), 3.23 (4H, q, *J* 5.6), 1.53 (4H, br s). δ_C [$(CD_3)_2SO$] 160.8, 150.3, 132.2, 131.9, 129.9, 129.2, 116.3, 106.4, 39.3, 26.2.

2-Cyano-N-*{4-[2-cyano-3-(3-hydroxyphenyl)acryloylamino]-butyl}-3-(3-hydroxyphenyl)acrylamide* ***31***

This was synthesized in the manner described for **5** from **4c** and 3-hydroxybenzaldehyde to yield a yellow solid (80%), mp 224–228°C.

δ_H [$(CD_3)_2SO$] 8.46 (2H, t, *J* 5.5), 8.03 (2H, s), 7.36 (4H, m), 7.32 (2H, s), 6.96 (2H, m), 3.22 (4H, br s), 1.52 (4H, br s). δ_C [$(CD_3)_2SO$] 160.9, 157.7, 150.4, 133.0, 130.2, 121.3, 119.5, 116.3, 115.7, 106.0, 39.3, 26.2.

2-Cyano-N-*{4-[2-cyano-3-(4-hydroxyphenyl)acryloylamino]-butyl}-3-(4-hydroxyphenyl)acrylamide* ***32***

This was synthesized in the manner described for **5** from **4c** and 4-hydroxybenzaldehyde to yield a yellow solid (80%), mp 290–292°C. δ_H [$(CD_3)_2SO$] 8.28 (2H, t, *J* 5.6), 8.01 (2H, s), 7.84 (4H, d, *J* 8.9), 6.90 (4H, d, *J* 8.8), 3.20 (4H, q, *J* 5.4), 1.49 (4H, br s). δ_C [$(CD_3)_2SO$] 161.7, 161.3, 150.2, 132.7, 122.8, 117.2, 116.1, 101.1, 39.3, 26.3.

2-Cyano-N-*{3-[2-cyano-3-(3,4-dihydroxyphenyl)acryloylamino]-butyl}-3-(3,4-dihydroxyphenyl)acrylamide* ***33***

This was synthesized in the manner described for **5** from **4c** and 3,4-dihydroxybenzaldehyde to yield a yellow solid (97%), mp 281°C (lit.[8] 283°C). δ_H [$(CD_3)_2SO$] 8.25 (2H, t, *J* 5.5), 7.91 (2H, s), 7.53 (2H, d, *J* 1.9), 7.26 (2H, dd, *J* 8.3 and 1.9), 6.85 (2H, d, *J* 8.3), 3.20 (4H, br s), 1.49 (4H, br s). δ_C [$(CD_3)_2SO$] 161.5, 150.9, 150.4, 145.7, 125.2, 123.1, 117.2, 115.8, 100.5, 39.3.

3-(2-Chlorophenyl)-N-*{4-[3-(2-chlorophenyl)-2-cyanoacryloylamino]butyl}-2-cyanoacrylamide* ***34***

This was synthesized in the manner described for **5** from **4c** and 2-chlorobenzaldehyde to yield a yellow solid (93%), mp 196–198°C. δ_H [$(CD_3)_2SO$] 8.61 (2H, t, *J* 5.6), 7.98 (2H, s), 7.63 (6H, dd, *J* 4.2 and 2.0), 7.56 (6H, m), 3.25 (4H, q, *J* 5.6), 1.54 (4H, br s). δ_C [$(CD_3)_2SO$] 159.9, 146.7, 134.0, 133.1, 130.3, 130.0, 129.6, 127.7, 115.3, 110.5.

3-(3-Chlorophenyl)-N-*{4-[3-(2-chlorophenyl)-2-cyanoacryloylamino]butyl}-2-cyanoacrylamide* ***35***

This was synthesized in the manner described for **5** from **4c** and 3-chlorobenzaldehyde to yield a yellow solid (73%), mp 202–204°C. δ_H [$(CD_3)_2SO$] 8.48 (2H, t, *J* 5.5), 8.14 (2H, s), 7.95 (2H, t, *J* 1.7), 7.85 (2H, m), 7.60 (4H, m), 3.25 (4H, q, *J* 5.6), 1.52 (4H, br s). δ_C [$(CD_3)_2SO$] 160.9, 157.7, 150.4, 133.0, 130.2, 121.3, 119.5, 116.3, 115.7, 106.0, 39.3, 26.2.

3-(4-Chlorophenyl)-N-*{4-[3-(4-chlorophenyl)-2-cyanoacryloylamino]butyl}-2-cyanoacrylamide* ***36***

This was synthesized in the manner described for **5** from **4c** and 4-chlorobenzaldehyde to yield a yellow solid (72%), mp 232–234°C. δ_H [$(CD_3)_2SO$] 8.47 (2H, t, *J* 5.4), 8.14 (2H, s), 7.93 (4H, d, *J* 6.9), 7.62 (4H, d, *J* 6.8), 3.23 (4H, q, *J* 5.5), 1.53 (4H, br s). δ_C [$(CD_3)_2SO$] 160.6, 149.0, 136.7, 131.6, 130.7, 129.3, 116.1, 107.0, 39.4, 26.2.

2-Cyano-N-*{4-[2-cyano-3-(3-methoxyphenyl)acryloylamino]-butyl}-3-(3-methoxyphenyl)acrylamide* ***37***

This was synthesized in the manner described for **5** from **4c** and 3-methoxybenzaldehyde to yield a yellow solid (89%), mp 180–182°C. δ_H [$(CD_3)_2SO$] 8.46 (2H, br t, *J* 5.6), 8.12 (2H, s), 7.45 (6H, m), 7.13 (2H, m), 3.78 (6H, s), 3.23 (4H, br s), 1.54 (4H, br s). δ_C [$(CD_3)_2SO$] 160.7, 159.3, 150.2, 133.1, 130.2, 122.3, 118.1, 116.3, 114.7, 106.6, 55.2, 39.3, 26.2.

2-Cyano-N-*{4-[2-cyano-3-(4-methoxyphenyl)acryloylamino]-butyl}-3-(4-methoxyphenyl)acrylamide* ***38***

This was synthesized in the manner described for **5** from **4c** and 4-methoxybenzaldehyde to yield a yellow solid (81%), mp 200–202°C. δ_H [$(CD_3)_2SO$] 8.32 (2H, t, *J* 5.6), 8.07 (2H, s), 7.94 (4H, d, *J* 8.9), 7.10 (4H, d, *J* 8.9), 3.83 (6H, s), 3.22 (4H, q, *J* 5.5), 1.52 (4H, br s). δ_C [$(CD_3)_2SO$] 162.4, 161.2, 149.8, 132.3, 124.4, 116.9, 114.7, 102.7, 55.5, 39.2, 26.3.

2-Cyano-N-*{4-[2-cyano-3-(3-hydroxy-4-methoxyphenyl)-acryloylamino]butyl}-3-(3-hydroxy-4-methoxyphenyl)-acrylamide* ***39***

This was synthesized in the manner described for **5** from **4c** and 3-hydroxy-4-methoxybenzaldehyde to yield a yellow solid (91%), mp 294–296°C. δ_H [$(CD_3)_2SO$] 8.28 (2H, t, *J* 5.5), 7.96 (2H, s), 7.52 (2H, d, *J* 1.9), 7.37 (2H, dd, *J* 8.5 and 1.8), 7.06 (2H, d, *J* 8.5), 3.84 (6H, s), 3.21 (2H, q, *J* 5.0), 1.51 (2H, br s). δ_C [$(CD_3)_2SO$] 161.3, 151.6, 150.1, 146.6, 124.5, 116.9, 115.4, 111.9, 102.2, 55.6, 39.3, 26.3.

2-Cyano-N-*{4-[2-cyano-3-(4-carboxyphenyl)acryloylamino]-butyl}-3-(4-carboxyphenyl)acrylamide* ***40***

This was synthesized in the manner described for **5** from **4c** and 4-carboxybenzaldehyde to yield a white solid (50%), mp 298–300°C. δ_H [$(CD_3)_2SO$] 8.59 (2H, t, *J* 5.3), 8.35 (4H, d, *J* 8.5), 8.27 (2H, s), 8.10 (4H, d, *J* 8.6), 3.25 (2H, q, *J* 4.9), 1.55 (2H, br s). δ_C [$(CD_3)_2SO$] 166.6, 160.5, 149.1, 135.5, 134.0, 129.8, 129.7, 116.0, 108.4, 39.5, 28.6.

2-Cyano-N-*[5-(2-cyano-3-phenylacryloylamino)pentyl]-3-phenylacrylamide* ***41***

This was synthesized in the manner described for **5** from **4d** and benzaldehyde to yield a yellow solid (51%), mp 164–166°C. δ_H [$(CD_3)_2SO$] 8.43 (2H, t, *J* 5.3), 8.14 (2H, s), 7.91 (4H, m), 7.55 (6H, m), 3.21 (4H, q, *J* 6.7), 1.52 (4H, quin, *J* 7.3), 1.31 (2H, quin, *J* 6.7). δ_C [$(CD_3)_2SO$] 160.8, 150.2, 132.1, 131.1, 129.9, 129.1, 116.3, 106.5, 39.5, 28.4, 23.7.

2-Cyano-N-*{5-[2-cyano-3-(3-hydroxyphenyl)acryloylamino]-pentyl}-3-(3-hydroxyphenyl)acrylamide* ***42***

This was synthesized in the manner described for **5** from **4d** and 3-hydroxybenzaldehyde to yield a yellow solid (92%), mp 230–232°C. δ_H [$(CD_3)_2SO$] 8.42 (2H, t, *J* 5.4), 8.02 (2H, s), 7.34 (4H, m), 7.31 (2H, s), 6.97 (2H, m), 3.19 (4H, q, *J* 6.0), 1.52 (4H, quin, *J* 7.0), 1.32 (2H, quin, *J* 6.8). δ_C [$(CD_3)_2SO$] 160.9, 157.7, 150.3, 133.0, 130.2, 121.3, 119.5, 116.3, 115.7, 106.1, 39.5, 28.4, 23.6.

2-Cyano-N-*{5-[2-cyano-3-(4-hydroxyphenyl)acryloylamino]-pentyl}-3-(4-hydroxyphenyl)acrylamide* ***43***

This was synthesized in the manner described for **5** from **4d** and 4-hydroxybenzaldehyde to yield a yellow solid (98%), mp 242–244°C. δ_H [$(CD_3)_2SO$] 8.24 (2H, t, *J* 5.5), 7.99 (2H, s) 7.84 (4H, d, *J* 8.8), 6.88 (4H, d, *J* 8.7), 3.18 (4H, q, *J* 6.9), 1.48 (4H, quin, *J* 7.3), 1.28 (2H, quin, *J* 6.8). δ_C [$(CD_3)_2SO$] 162.0, 161.4, 150.1, 132.7, 122.6, 117.2, 116.2, 101.0, 39.5, 28.5, 23.7.

2-Cyano-N-*{3-[2-cyano-3-(3,4-dihydroxyphenyl)acryloylamino]-pentyl}-3-(3,4-dihydroxyphenyl)acrylamide* ***44***

This was synthesized in the manner described for **5** from **4d** and 3,4-dihydroxybenzaldehyde to yield a yellow solid (90%), mp 252°C (lit.[8] 248°C). δ_H [$(CD_3)_2SO$] 8.15 (2H, t, *J* 5.5), 7.85 (2H, s), 7.50 (2H, d, *J* 2.1), 7.20 (2H, dd, *J* 8.5 and 2.0), 6.75 (2H, d, *J* 8.5), 3.16 (4H, q, *J* 6.2), 1.50 (4H, quin, *J* 7.1), 1.28 (2H, quin, *J* 6.9). δ_C [$(CD_3)_2SO$] 161.9, 153.9, 150.3, 146.3, 126.2, 121.5, 117.7, 115.7, 114.7, 98.4, 39.5, 28.6, 23.7

2-Cyano-N-*{5-[2-cyano-3-(3,4-dimethoxyphenyl)acryloylamino]-pentyl}-3-(3,4-dimethoxyphenyl)acrylamide* ***45***

This was synthesized in the manner described for **5** from **4d** and 3,4-dimethoxybenzaldehyde to yield a yellow solid (80%), mp > 300°C. δ_H [$(CD_3)_2SO$] 8.28 (2H, t, *J* 5.5), 8.05 (2H, s), 7.61 (2H, dd, *J* 1.9), 7.54 (2H, dd, *J* 8.5 and 1.8), 7.10 (2H, d, *J* 8.6), 3.83 (6H, s), 3.78 (6H, s), 3.20 (4H, q, *J* 6.1), 1.51 (4H, quin, *J* 7.1), 1.31 (2H, quin, *J* 6.8). δ_C [$(CD_3)_2SO$] 161.1, 152.3, 150.1, 148.5, 125.2, 124.4, 117.1, 112.2, 110.7, 102.6, 55.7, 55.3, 55.3, 39.4, 28.5, 23.6.

3-(2-Chlorophenyl)-N-*{5-[3-(2-chlorophenyl)-2-cyanoacryloylamino]pentyl}-2-cyanoacrylamide* ***46***

This was synthesized in the manner described for **5** from **4d** and 2-chlorobenzaldehyde to yield a yellow solid (96%), mp 164–166°C. δ_H [$(CD_3)_2SO$] 8.56 (2H, t, *J* 5.5), 8.34 (2H, s), 7.98 (2H, m), 7.54 (6H, m), 3.23 (4H, q, *J* 6.1), 1.55 (4H, quin, *J* 7.0), 1.32 (2H, quin, *J* 6.7). δ_C [$(CD_3)_2SO$] 159.9, 146.6, 134.0, 133.1, 130.3, 129.9, 129.6, 127.7, 115.4, 110.5, 39.6, 28.4, 23.7.

3-(2-Chlorophenyl)-N-*{5-[3-(3-chlorophenyl)-2-cyanoacryloylamino]pentyl}-2-cyanoacrylamide* ***47***

This was synthesized in the manner described for **5** from **4d** and 3-chlorobenzaldehyde to yield a yellow solid (63%), mp 158–160°C. δ_H [$(CD_3)_2SO$] 8.42 (2H, t, *J* 5.4), 8.12 (2H, s), 7.94 (2H, t, *J* 1.6), 7.85 (2H, m), 7.58 (2H, m), 3.20 (4H, q, *J* 6.7), 1.52 (4H, quin, *J* 7.2), 1.32 (2H, quin, *J* 5.2). δ_C [$(CD_3)_2SO$] 160.4, 148.6, 133.9, 133.7, 131.6, 130.9, 129.2, 128.3, 128.2, 115.9, 108.1, 39.2, 28.3, 23.6

3-(4-Chlorophenyl)-N-*{5-[3-(4-chlorophenyl)-2-cyanoacryloylamino]pentyl}-2-cyanoacrylamide* ***48***

This was synthesized in the manner described for **5** from **4d** and 4-chlorobenzaldehyde to yield a yellow solid (84%), mp 160–162°C. δ_H [$(CD_3)_2SO$] 8.45 (2H, t, *J* 5.3), 8.12 (2H, s), 7.90 (4H, d, *J* 6.9), 7.60 (4H, d, *J* 8.6), 3.20 (4H, q, *J* 6.0), 1.51 (4H, quin, *J* 7.1), 1.32 (2H, quin, *J* 6.7). δ_C [$(CD_3)_2SO$] 160.6, 148.8, 136.7, 131.5, 130.7, 129.2, 116.1, 107.0, 39.5, 28.4, 23.6.

2-Cyano-N-*{5-[2-cyano-3-(3-methoxyphenyl)acryloylamino]-pentyl}-3-(3-methoxyphenyl)acrylamide* ***49***

This was synthesized in the manner described for **5** from **4d** and 3-methoxybenzaldehyde to yield a yellow solid (96%), mp 124–126°C. δ_H [$(CD_3)_2SO$] 8.43 (2H, t, *J* 5.6), 8.10 (2H, s), 7.47 (6H, m), 7.13 (2H, m), 3.79 (6H, s) 3.21 (4H, q, *J* 6.7), 1.51 (4H, quin, *J* 7.1), 1.32 (2H, quin, *J* 6.7). δ_H [$(CD_3)_2SO$] 160.7, 159.3, 150.1, 133.1, 130.2, 122.3, 118.0, 116.3, 114.7, 106.7, 55.2, 39.5, 28.4, 23.6.

2-Cyano-N-*{5-[2-cyano-3-(4-methoxyphenyl)acryloylamino]-pentyl}-3-(4-methoxyphenyl)acrylamide* ***50***

This was synthesized in the manner described for **5** from **4d** and 4-methoxybenzaldehyde to yield a yellow solid (87%), mp 132–134°C. δ_H [$(CD_3)_2SO$] 8.30 (2H, t, *J* 5.6), 8.06 (2H, s), 7.94 (4H, d, *J* 8.9), 7.08 (4H, d, *J* 8.9), 3.83 (6H, s), 3.20 (4H, q, *J* 6.0), 1.50 (4H, quin, *J* 7.1), 1.30 (4H, quin, *J* 5.6). δ_C [$(CD_3)_2SO$] 162.4, 161.1, 149.7, 132.3, 124.4, 116.9, 114.7, 102.7, 55.5, 39.5, 28.5, 23.6.

2-Cyano-N-*{5-[2-cyano-3-(3-hydroxy-4-methoxyphenyl)-acryloylamino]pentyl}-3-(3-hydroxy-4-methoxyphenyl)-acrylamide* ***51***

This was synthesized in the manner described for **5** from **4d** and 3-hydroxy-4-methoxybenzaldehyde to yield a yellow solid (92%), mp 196–198°C. δ_H [$(CD_3)_2SO$] 8.27 (2H, t, *J* 5.5), 7.94 (2H, s), 7.51 (2H, d, *J* 2.2), 7.36 (2H, dd, *J* 8.6 and 2.2), 7.05 (2H, d, *J* 8.6), 3.84 (6H, s), 3.19 (2H, q, *J* 6.6), 1.50 (2H, quin, *J* 7.0), 1.29 (2H, quin, *J* 4.7). δ_C [$(CD_3)_2SO$] 161.3, 151.6, 150.0, 146.6, 124.5, 116.9, 115.4, 111.9, 102.3, 55.6, 39.5, 28.5, 23.7.

2-Cyano-N-*{5-[2-cyano-3-(4-carboxyphenyl)acryloylamino]-pentyl}-3-(4-carboxyphenyl)acrylamide* ***52***

This was synthesized in the manner described for **5** from **4d** and 4-carboxybenzaldehyde to yield a yellow solid (74%), mp 226–228°C. δ_H [$(CD_3)_2SO$] 8.52 (2H, t, *J* 5.1), 8.18 (2H, s), 8.03 (4H, d, *J* 8.9), 7.98 (4H, d, *J* 8.9), 3.21 (4H, q, *J* 6.4), 1.54 (4H, quin, *J* 6.9), 1.32 (2H, quin, *J* 4.9). δ_C [$(CD_3)_2SO$] 166.6, 160.5, 149.1, 135.5, 134.0, 129.8, 129.7, 115.9, 108.4, 39.5, 28.4, 23.6.

2-Cyano-N-*[6-(2-cyano-3-phenylacryloylamino)-hexyl]-3-phenylacrylamide* ***53***

This was synthesized in the manner described for **5** from **4e** and benzaldehyde to yield a yellow solid (72%), mp 166–168°C. δ_H [$(CD_3)_2SO$] 8.43 (2H, t, *J* 5.5), 8.14 (2H, s), 7.91 (4H, m), 7.54 (6H, m), 3.21 (4H, quin, *J* 6.3), 1.50 (4H, quin, *J* 6.2), 1.31 (4H, br quin, *J* 6.4). δ_C [$(CD_3)_2SO$] 160.7, 150.2, 132.1, 131.9, 129.9, 129.1, 116.3, 106.5, 39.6, 28.7, 26.0.

2-Cyano-N-*{6-[2-cyano-3-(3-hydroxyphenyl)acryloylamino]-hexyl}-3-(3-hydroxyphenyl)acrylamide* ***54***

This was synthesized in the manner described for **5** from **4e** and 3-hydroxybenzaldehyde to yield a white solid (70%), mp 234–236°C. δ_H [$(CD_3)_2SO$] 8.39 (2H, t, *J* 5.5), 8.02 (2H, s), 7.33 (6H, m), 6.96 (2H, m), 3.18 (4H, q, *J* 6.1), 1.50 (4H, br quin, *J* 6.1), 1.30 (4H, br quin, *J* 6.2). δ_C [$(CD_3)_2SO$] 160.8, 157.7, 150.2, 133.0, 130.2, 121.3, 119.5, 116.3, 115.7, 106.1, 39.6, 28.7, 26.0.

2-Cyano-N-*{6-[2-cyano-3-(4-hydroxyphenyl)acryloylamino]-hexyl}-3-(4-hydroxyphenyl)acrylamide* ***55***

This was synthesized in the manner described for **5** from **4e** and 4-hydroxybenzaldehyde to yield a yellow solid (65%), mp 272–276°C. δ_H [$(CD_3)_2SO$] 8.21 (2H, t, *J* 5.4), 8.00 (2H, s), 7.84 (4H, d, *J* 8.7), 6.90 (4H, d, *J* 8.5), 3.18 (4H, q, *J* 6.2), 1.48 (4H, br quin, *J* 6.0), 1.29 (4H, br quin, *J* 6.3). δ_C [$(CD_3)_2SO$] 161.7, 161.3, 150.1, 132.7, 132.7, 122.8, 117.2, 116.1, 101.2, 39.5, 28.8, 26.0.

2-Cyano-N-*{3-[2-cyano-3-(3,4-dihydroxyphenyl)acryloylamino]-hexyl}-3-(3,4-dihydroxyphenyl)acrylamide* ***56***

This was synthesized in the manner described for **5** from **4e** and 3,4-dihydroxybenzaldehyde to yield a yellow solid (89%), mp 263°C (lit.[8] 260°C). δ_H [$(CD_3)_2SO$] 8.18 (2H, t, *J* 5.5), 7.89 (2H, s), 7.51 (2H, d, *J* 2.0), 7.24 (2H, dd, *J* 2.0 and 8.3), 6.83 (2H, d, *J* 8.3), 3.17 (4H, q, *J* 6.1), 1.47 (4H, quin, *J* 6.1), 1.28 (4H, br s). δ_C [$(CD_3)_2SO$] 161.5, 151.2, 150.3, 145.7, 125.2, 122.9, 117.2, 115.8, 115.7, 100.4, 39.5, 28.8, 26.0.

3-(2-Chlorophenyl)-N-*{6-[3-(2-chlorophenyl)-2-cyanoacryloylamino]hexyl}-2-cyanoacrylamide* ***57***

This was synthesized in the manner described for **5** from **4e** and 2-chlorobenzaldehyde to yield a yellow solid (91%), mp 160–162°C. δ_H [$(CD_3)_2SO$] 8.56 (2H, t, *J* 5.5), 8.33 (2H, s), 7.98 (2H, m), 7.56 (6H, m), 3.22 (4H, q, *J* 6.3), 1.52 (4H, quin, *J* 5.9), 1.32 (4H, br quin, *J* 6.2). δ_C [$(CD_3)_2SO$] 159.9, 146.6, 134.0, 133.1, 130.4, 130.0, 129.6, 127.7, 115.3, 110.6, 39.7, 28.6, 26.0.

3-(2-Chlorophenyl)-N-*{6-[3-(2-chlorophenyl)-2-cyanoacryloylamino]hexyl}-2-cyanoacrylamide* ***58***

This was synthesized in the manner described for **5** from **4e** and 3-chlorobenzaldehyde to yield a yellow solid (85%), mp 192–194°C. δ_H [$(CD_3)_2SO$] 8.44 (2H, t, *J* 5.5), 8.13 (2H, s), 7.95 (2H, t, *J* 1.8), 7.85 (2H, m), 7.61 (2H, m), 3.19 (4H, q, *J* 6.8), 1.51 (4H, quin, *J* 6.5), 1.30 (4H, br quin, *J* 6.4). δ_C [$(CD_3)_2SO$] 160.4, 148.6, 134.0, 133.7, 131.6, 131.0, 129.2, 128.3, 115.9, 108.2, 39.2, 28.61, 25.9.

3-(4-Chlorophenyl)-N-*{6-[3-(4-chlorophenyl)-2-cyanoacryloylamino]hexyl}-2-cyanoacrylamide* ***59***

This was synthesized in the manner described for **5** from **4e** and 4-chlorobenzaldehyde to yield a yellow solid (72%), mp 198–200°C. δ_H [$(CD_3)_2SO$] 8.45 (2H, t, *J* 5.3), 8.12 (2H, s), 7.92 (2H, d, *J* 6.9), 7.62 (2H, d, *J* 6.9), 3.20 (4H, quin, *J* 6.2), 1.50 (4H, quin, *J* 6.0), 1.31 (4H, br quin, *J* 6.0). δ_C [$(CD_3)_2SO$] 160.5, 148.9, 136.7, 131.5, 130.8, 129.2, 116.0, 107.0, 39.6, 28.6, 26.0.

2-Cyano-N-*{6-[2-cyano-3-(3-methoxyphenyl)acryloylamino]-hexyl}-3-(3-methoxyphenyl)acrylamide* ***60***

This was synthesized in the manner described for **5** from **4e** and 3-methoxybenzaldehyde to yield a yellow solid (77%), mp 136–138°C.

δ_H [$(CD_3)_2SO$] 8.42 (2H, t, *J* 5.5), 8.12 (2H, s), 7.46 (6H, m), 7.14 (2H, m), 3.80 (6H, s), 3.22 (4H, q, *J* 6.0), 1.51 (4H, br quin, *J* 6.1), 1.31 (4H, br quin, *J* 6.1). δ_C [$(CD_3)_2SO$] 160.7, 159.3, 150.1, 133.1, 130.2, 122.3, 118.0, 116.3, 114.7, 106.7, 55.2, 39.6, 28.7, 26.0.

2-Cyano-N-*{6-[2-cyano-3-(4-methoxyphenyl)acryloylamino]-hexyl}-3-(4-methoxyphenyl)acrylamide* ***61***

This was synthesized in the manner described for **5** from **4e** and 4-methoxybenzaldehyde to yield a yellow solid (98%), mp 182–184°C. δ_H [$(CD_3)_2SO$] 8.29 (2H, t, *J* 5.5), 8.06 (2H, s), 7.93 (2H, d, *J* 7.2), 7.11 (2H, d, *J* 7.2), 3.84 (6H, s), 3.17 (4H, q, *J* 5.7), 1.49 (4H, br quin, *J* 5.9), 1.30 (4H, br quin, *J* 6.2). δ_C [$(CD_3)_2SO$] 162.4, 161.0, 149.7, 132.23, 124.4, 116.9, 114.7, 102.7, 55.5, 39.5, 28.7, 26.0.

2-Cyano-N-*{6-[2-cyano-3-(3-hydroxy-4-methoxyphenyl)-acryloylamino]hexyl}-3-(3-hydroxy-4-methoxyphenyl)-acrylamide* ***62***

This was synthesized in the manner described for **5** from **4e** and 3-hydroxy-4-methoxybenzaldehyde to yield a yellow solid (99%), mp 226–228°C. δ_H [$(CD_3)_2SO$] 8.26 (2H, t, *J* 5.6), 7.95 (2H, s), 7.52 (2H, d, *J* 1.9), 7.36 (2H, dd, *J* 8.2 and 1.9), 7.06 (2H, d, *J* 8.2), 3.84 (6H, s), 3.18 (4H, q, *J* 5.8), 1.49 (4H, br quin, *J* 6.0), 1.29 (4H, br quin, *J* 5.9). δ_C [$(CD_3)_2SO$] 161.3, 151.6, 150.1, 146.7, 124.6, 124.5, 116.9, 115.4, 111.9, 102.3, 55.6, 39.5, 28.8, 26.0.

2-Cyano-N-*{6-[2-cyano-3-(4-carboxyphenyl)acryloylamino]-hexyl}-3-(4-carboxyphenyl)acrylamide* ***63***

This was synthesized in the manner described for **5** from **4e** and 4-carboxybenzaldehyde to yield a yellow solid (67%), mp 288–292°C. δ_H [$(CD_3)_2SO$] 8.53 (2H, t, *J* 5.1), 8.18 (2H, s), 8.07 (4H, d, *J* 8.3), 7.98 (4H, d, *J* 8.3), 3.20 (4H, q, *J* 5.8), 1.51 (4H, br s), 1.31 (4H, br s). δ_C [$(CD_3)_2SO$] 166.6, 160.5, 149.1, 135.5, 134.0, 129.8, 129.7, 116.0, 108.4, 39.5, 28.6, 26.0.

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